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Original Research

Factors affecting mortality in patients with tuberculosis and the impact of the pandemic on patient follow-up

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Abstract

Aim: Tuberculosis (TB) remains one of the leading causes of mortality worldwide. In this study, we aimed to evaluate the patients who were followed up with a diagnosis of TB in the last five years, examine the factors associated with mortality in these patients, and investigate the effect of the pandemic on patient follow-up.

Material and Methods: The data of the patients who were followed up at the Tuberculosis Dispensary between June 1, 2017, and June 1, 2022, with a diagnosis of TB were retrospectively analyzed.

Results: The study included 395 patients with a mean age of 49.6±20.2 years who were followed up with a diagnosis of TB for five years. Of the patients, 208 (52.7%) were male and 187 (47.3%) were female. Pulmonary involvement was found in 160 (40.5%) and non-pulmonary involvement in 212 (53.7%) patients. Follow-up of 11.1% of patients resulted in death. The mean age of the deceased (65.1±16.9) was significantly higher ($p<0.001$), and there was no significant difference in mortality between both sexes ($p=0.957$). While the number of patients diagnosed before the pandemic was 219 (55.4%), it was 176 (44.6%) during the pandemic period and there was no difference between the two periods in terms of mortality.

Discussion: Patients over 61 years of age and those with pulmonary + non-pulmonary or pulmonary involvement had significantly higher mortality; therefore, a great deal of care should be taken to avoid delays in diagnosis and treatment, particularly for elderly patients. During the pandemic, the number of patients diagnosed has decreased due to disruptions in health services, so the number of cases and deaths due to TB may increase in the coming years. It is of great importance to take effective measures for disease control and to raise awareness on this issue.

Keywords

Tuberculosis, Pandemic, Mortality, Treatment

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Introduction

Tuberculosis (TB) has been a major cause of illness and death in human society since ancient times. TB dates back to approximately 3.3 million years ago. After reaching epidemic levels in Europe and North America in the eighteenth and nineteenth centuries, TB declined in developed countries in the twentieth century, but continues to be a serious threat in low-middle-income and developing countries, particularly due to the emergence of drug-resistant strains and the increasing association with human immunodeficiency virus (HIV) [1,2].

TB is an infectious disease caused by Mycobacterium tuberculosis, a gram-positive, aerobic, non-spore bacillus, most commonly affecting the lungs. The causative microorganism is airborne and reaches the lungs through inhalation of bacilli spread by coughing, sneezing, and talking of an infected person. Immediate diagnosis and initiation of effective treatment are vital in terms of prevention of transmission and control of the disease [3]. However, since common clinical manifestations of TB such as cough, fever, malaise, and weight loss are also seen in many other diseases, there may be delays in diagnosis and treatment.

According to the World Health Organization (WHO), TB is the largest cause of death from a single infectious agent and the 13th leading cause of death worldwide. In 2020, TB ranked second only to COVID-19 as a cause of death from a single infectious agent. According to the estimate in the "2022 Global Tuberculosis Report", 10.6 million people contracted TB and 1.6 million people died from TB in 2021 (including 187 000 people who were HIV positive), an increase of 4.5% compared to 2020. The burden of drug-resistant tuberculosis (DR-TB) also increased by 3% between 2020 and 2021, with 450 000 new cases of rifampicin-resistant TB (RR-TB) in 2021. For the first time in many years, an increase in the number of people infected with TB and DR-TB has been reported. As with many other healthcare services, TB services have been disrupted by the COVID-19 pandemic, but its impact on the fight against TB has been particularly severe. Ongoing conflicts in Eastern Europe, Africa, and the Middle East have made poor populations more vulnerable (Available at: https://www.who.int/publications/i/item/9789240037021).

Globally, there is concern about increases in the number of patients and TB-related deaths compared to previous years as a result of the disruption of healthcare services due to the pandemic. Turkey has been receiving large numbers of migrants from these regions in recent years due to the wars in its geography. Immigrants who have not been able to access healthcare services sufficiently due to war, poverty, and the pandemic are a high-risk group in terms of TB transmission. As a result of this risky migration wave, the number of cases and deaths in the country is likely to increase. Raising awareness on this issue, especially in primary health care facilities, knowing the characteristics of the disease, preventing delays in diagnosis and treatment, and controlling the spread of the disease will be useful. In this study, we aimed to evaluate the TB patients diagnosed and followed up in the last five years in our province, to examine the factors affecting mortality and the effects of the pandemic on patient follow-up.

Material and Methods

In this cross-sectional study, we retrospectively analyzed the records of patients who were followed up with a diagnosis of TB in the Afyonkarahisar Tuberculosis Dispensary between June 1, 2017, and June 1, 2022. The pandemic period was considered to be 2020, 2021, and 2022, while the pre-pandemic period was considered to be 2019, 2018, and 2017. Demographic characteristics of the patients, sites of TB involvement, diagnostic methods, treatment modalities, treatment durations, treatment outcomes, TB incidence, and distribution of patients according to age and sex were analyzed. Patients under the age of 18 years were considered to be in the pediatric age group.

Statistical Analysis

Statistical analysis of the data was conducted via SPSS version 22 software. Number, percentage, mean, standard deviation, minimum and maximum values, and independent sample t-tests were used to analyze the research data in the computer environment.

In the bivariate analysis, a multivariate logistic regression model was established with the variables of age and site of TB involvement, which showed statistically significant differences in mortality. The cut-off value for significance was $p<0.05$.

Ethics Committee Approval

The study was approved by the Health Sciences University Clinical Research Ethics Committee (Decision No: 2022/394 and dated 05-08-2022).

Results

In the study, 395 TB patients who were followed up between June 2017 and June 2022 and whose records could be accessed in Afyonkarahisar Tuberculosis Dispensary were evaluated. Of the patients, 208 (52.7%) were male and 187 (47.3%) were female with a mean age of 49.6±20.2 years. Three hundred and seventy-six (95.2%) patients were newly diagnosed with TB, while 19 (4.8%) patients had a relapse. Thirty-two (8.1%) patients were in the pediatric age group, and none of them developed mortality. HIV positivity was detected in only one patient (0.3%). Of the patients, 363 (91.9%) were citizens of the Republic of Turkey, and 32 (8.1%) were immigrants (3.8% from Afghanistan, 3.0% from Syria, and 1.3% other immigrants). Patients with pulmonary involvement accounted for 160 (40.5%) patients, while patients with non-pulmonary involvement made up the majority (212, 53.7%). Pulmonary + non-pulmonary involvement was present in 12% of patients. Socio-demographic characteristics and sites of involvement are presented in Table 1.

The diagnosis was most commonly made by histopathologic examination (209, 52.9%). In addition, 102 (25.8%) were diagnosed due to smear positivity and 28 (7.1%) due to culture positivity, while 57 (14.4%) were diagnosed clinically and radiologically. In 15 (3.8%) patients, other diagnostic methods such as the Quantiferon TB-Gold test and polymerase chain reaction (PCR) were used for diagnosis.

While first-line drug therapy (isoniazid, rifampicin, pyrazinamide, ethambutol) was given to 374 (94.7%) patients in the treatment, second-line drug treatments were given to 15 (3.8%) patients due to the development of side effects

Table 1. Sociodemographic characteristics of patients and sites of involvement.

	Pulmonary TB n(%)	Non-pulmonary TB n(%)	Pulmonary+Non-pulmonary TB n(%)	p
Sex				
Female	53(28.3)	118(63.1)	16(8.6)	<0.001
Male	107(51.4)	94(45.2)	7(3.4)	
Age				
0-20	8(21.2)	28(73.7)	2(5.3)	0.033
21-40	33(35.5)	58(62.4)	2(2.2)	
41-60	53(41.4)	65(50.8)	10(7.8)	
61-80	56(47.9)	54(46.2)	7(6)	
81<	10(52.6)	7(36.8)	2(10.5)	
Nationality				
TR	145(39.9)	199(54.8)	19(5.2)	0.128
Foreigner	15(46.9)	13(40.6)	4(12.5)	

Table 2. Evaluation of patients according to mortality status.

	Mortal n(%)	Not mortal n(%)	p
Sex			
Female	21(11.2)	166(88.8)	0.957
Male	23(11.1)	185(88.9)	
Age			
0-20	--	38(100)	<0.001
20-40	4(4.3)	89(95.7)	
41-60	11(8.6)	117(91.4)	
61-80	20(17.1)	97(82.9)	
81<	9(47.4)	10(52.6)	
Nationality			
TR	43(11.8)	320(88.2)	0.133
Foreigner	1(3.1)	31(96.9)	
Site of involvement			
Pulmonary TB	27(16.9)	133(83.1)	0.001
Non-pulmonary TB	12(5.7)	200(94.3)	
Pulmonary+Non-pulmonary TB	5(21.7)	18(78.3)	

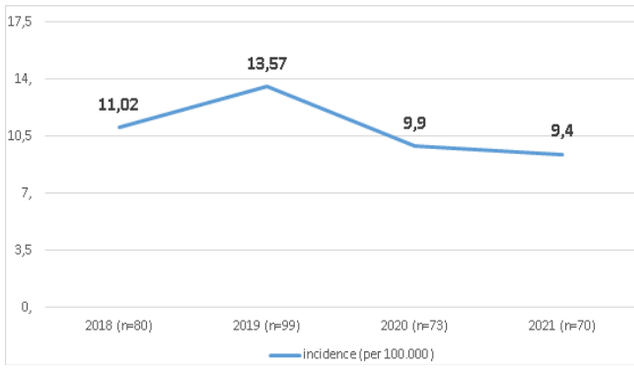

Figure 1. Tuberculosis incidence by year (2018-2021).

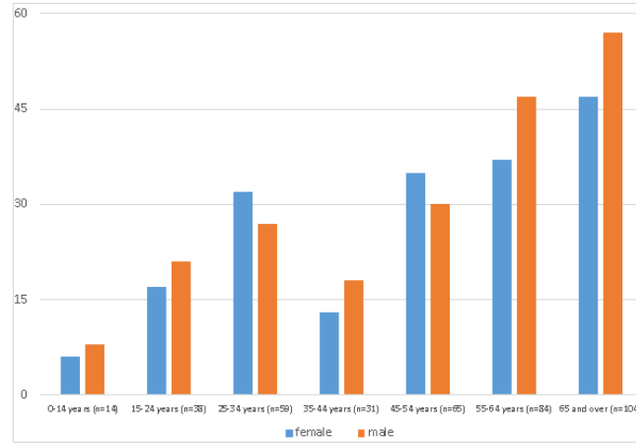

Figure 2. Distribution of patients by age and sex.

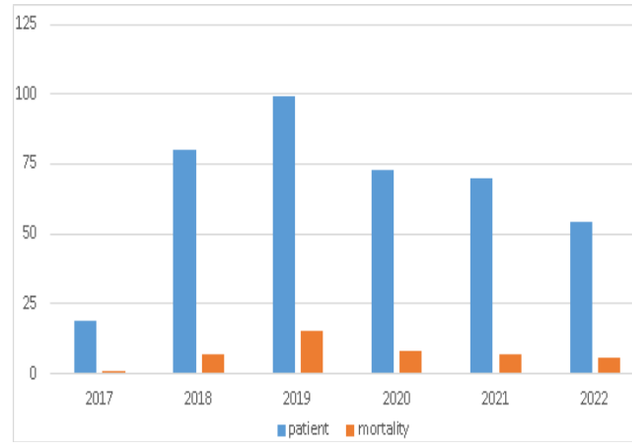

Figure 3. Number of patients and deaths by years.

Table 3. Factors affecting mortality according to logistic regression analysis results.

Variables	Univariate logistics				Multiple logistics			
	OR	95% CI		p-value	OR	95% CI		p-value
		Minimum	Maximum			Minimum	Maximum	
Site of involvement*								
Pulmonary TB	3.38	1.65	6.91	0.001	2.83	1.36	5.89	0.005
Pulmonary/ Non-pulmonary TB	4.63	1.46	14.61	0.009	3.88	1.18	12.78	0.025
Age*								
41-60	2.98	0.92	9.63	0.067	2.53	0.77	8.28	0.123
≥61	8.60	2.93	25.25	<0.001	7.18	2.42	21.31	<0.001

OR: Odds ratio, CI: Confidence interval; *: Non-pulmonary TB and age from 0 to 40 were considered as references. R^2=0.083, p<0.001

(n=6, 1.5%), multi-drug resistance (n=3, 0.7%) and insufficient pyrazinamide stock status (n=6, 1.5%). The clinical follow-up of 5 (1.2%) of 6 (1.5%) patients who refused to receive treatment resulted in death. It was determined that 69.4% of the patients in whom treatment was initiated completed the treatment, 15.7% were cured, and 11.1% died during the follow-up period. Of the deaths, 89.1% (41 people) occurred within the first 6 months after diagnosis, and the mean age of those who died (65.1±16.9) was significantly higher than that of survivors (47.7±19.7) ($p < 0.001$). When mortality rates were compared, no significant difference was found between the male and female gender ($p=0.957$). Characteristics of the patients according to mortality status are presented in Table 2. The results of the multivariate analysis revealed that the site of TB involvement and age affected mortality. While mortality was significantly higher in people aged 61 and above compared to those aged 0-40, mortality was significantly higher in pulmonary + non-pulmonary TB or pulmonary TB compared to non-pulmonary TB (Table 3).

Among the extrapulmonary sites involved, extrathoracic lymphadenopathy (LAP) (32.3%) and pleural involvement (16.6%) ranked first and second, respectively, while intrathoracic lymphadenopathy (9.3%) was the third most prevalent. In addition, 17 (7.3%) of the patients had gastrointestinal, 15 (6.4%) vertebral, 15 (6.4%) skin, 14 (6%) genitourinary, 8 (3.4%) nonvertebral bone joint involvement, 6 (2.5%) patients had TB meningitis. While the incidence of TB in our province was 11.0 per 100,000 in 2018, it increased to 13.6 per 100,000 in 2019, and it was observed that the incidence decreased significantly in 2020 and 2021 (Figure 1). TB was more common in older age and in males (Figure 2). The highest number of patients and deaths occurred in 2019 (Figure 3).

During the pandemic, 176 (44.6%) patients were diagnosed with TB compared to 219 (55.4%) before the pandemic. Meanwhile, the number of patients who died was 26 (11.9%) before the pandemic and 18 (10.2%) during the pandemic. Mortality rates during the pandemic period were not significantly different from those during the pre-pandemic period ($p=0.606$).

Discussion

In this study, we analyzed the data and mortality status of 395 patients who were followed up with a diagnosis of TB between June 2017 and June 2022 in our province. The mean age in the study was similar to the literature data. WHO reports that the majority of TB cases (70%) occur between the ages of 15-54. In similar studies conducted in Turkey, it was observed that tuberculosis was detected more frequently in middle-aged people. [4,5]. It is well-documented that TB is more common in males than in females in Turkey as well as in the world [6]. In this study, similar to the literature data, the proportion of males was higher.

Effective disease management is one of the critical components of TB control. TB patients are reported within 24 hours after diagnosis and patients are referred to the local TB Dispensary for follow-up and treatment, where treatment, follow-up, vaccination, contact screening, education, and counseling services are provided free of charge. The Directly Observed Therapy (DOT) strategy, recommended by the World Health Organization to increase treatment success and survival, started to be implemented in health institutions in Turkey in 2006. TB mortality is a significant indicator to assess the effectiveness of TB control programs and to quantify the burden of TB. Investigating risk factors associated with mortality in TB is essential to improve survival. WHO defines TB-related deaths as the number of TB patients who die during treatment, regardless of the actual cause of death. Despite differences across countries, various studies evaluating risk factors for mortality during TB treatment have suggested that factors such as age, sex, comorbidities, and HIV infection may be associated with mortality [7,8]. In Turkey, several studies have been conducted on the characteristics of TB-related mortality and associated risk factors.

In the present study, no significant difference was found between male and female sex in terms of mortality ($p=0.957$). Although the role of sex in mortality varies across studies, male sex has been defined as an independent risk factor for TB-related mortality in some studies [9]. On the other hand, in many studies, no significant difference has been found between surviving and deceased patients in terms of sex [10]. In a study investigating the factors associated with mortality in TB patients in Turkey, 382 patients with a median age of 54.0 years (34.0-67.0) were examined. 62% of the study group were males and male patients were found to be more common in the deceased patient group. It was also found that while treatment was successful in 90.6% of patients, 51.6% of those with a mortal course were over 70 years of age, and pulmonary TB was significantly more common in patients who died [11]. The results of the study, which found that mortality in pulmonary TB or pulmonary + non-pulmonary TB is higher compared to non-pulmonary TB, are consistent with the literature in this regard.

The most common mortality occurred in patients over 61 years of age, whereas the pediatric population had no mortality, and there was no significant difference between immigrant and Turkish patients in terms of mortality. In numerous studies, advancing age has been reported as a risk factor for mortality in TB patients [8,12]. High mortality in elderly patients may be due to comorbidities that increase with advancing age and factors such as weakened immune system responses, lack of awareness, association of symptoms with old age, and delayed hospital admissions. Therefore, TB screening in the elderly should be performed without delay whenever possible for early detection, diagnosis, and treatment.

There was a significant decrease in TB incidence during the pandemic period compared to the pre-pandemic period. However, there was no significant difference between the two periods in terms of mortality. In 2020, the COVID-19 pandemic significantly disrupted essential healthcare services, including the follow-up and treatment of TB patients. While the negative consequences of this especially on the poor and disadvantaged populations were felt more severely, reports of tuberculosis people decreased by 18% in 2020 compared to the previous year, and the number of estimated TB deaths increased for the first time in 9 years [13]. According to the Global Tuberculosis Report 2022, which covers more than 99% of the world's population and presents data reported from 202 countries and regions, the COVID-19 pandemic adversely affected

the diagnosis and care of TB, which increased the burden of the disease and caused the slowdown, interruption and even reversal of the progress made in the fight against TB until 2019. However, during the pandemic, the use of masks and adherence to social distancing measures contributed to a reduction in community transmission of TB. Due to the restrictions applied from time to time, lock-down measures, health policies giving priority to the fight against COVID-19, and using financial and human resources more in this area, and people refraining from applying to health institutions that are considered to be risky in terms of COVID-19 transmission, health services for the diagnosis and treatment of TB could not reach many people. Ultimately, newly diagnosed TB cases fell from 7.1 million in 2019 to 5.8 million in 2020. In 2021, this figure increased to 6.4 million but remained below pre-pandemic numbers [14]. Based on a similar study conducted in Turkey, it was found that TB incidence decreased significantly during the pandemic period [4]. The fact that the number of cases detected in our study decreased compared to the pre-pandemic period, as is the case worldwide, suggests that there is an increase in undiagnosed and untreated TB cases, which may lead to the spread of the infection in the community and an increase in deaths in the coming years. In order to correct this pessimistic picture and continue towards the global TB control targets, public health policies should be reconsidered as soon as possible and financial funds should be allocated to effectively fight TB. Furthermore, new and effective health service models should be developed to ensure uninterrupted access to health services, particularly for populations at-risk, and prompt diagnosis and treatment of TB.

Conclusion

In conclusion, since age 61 years or older and pulmonary or pulmonary + non-pulmonary involvement are associated with mortality, the diagnosis and treatment of these patients should not be delayed, and diagnostic tests should be performed immediately in case of clinical suspicion, especially in elderly patients, and effective treatment should be started. The number of TB patients diagnosed during the pandemic period has decreased compared to the pre-pandemic period. Since this situation will hinder the control of the disease, patients who cannot be detected in this period may spread the infection in the community and may cause an increase in the number of patients and deaths in the next few years.

Limitations

The retrospective study design is the most important limitation of this study. Data such as socioeconomic status, comorbidities, dietary habits, and admission symptoms of the patients could not be obtained. Prospective studies that take all these factors into account are needed to reach a more definitive conclusion.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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